

ANIMAL MODELS**Neuropeptides and social behavior: animal models relevant to autism**

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While it is tempting to assume that complex neuropsychiatric disorders involving disturbances in social interactions, social communication, and social cognition, such as autism, can only be properly investigated in humans, even a disorder of primarily social and higher cognitive processes is accompanied by certain features amenable to investigation in non-human species. The investigation of the neurobiological mechanisms underlying normal social behavior in animal models may provide insights into the neuropathology of these disorders. Here we present studies on two animal models that suggest that the neuropeptides oxytocin and vasopressin play an important role in the regulation of affiliation, social attachment and social recognition. Based on these studies, both neuropeptides and their respective receptors should be considered candidates contributing to the behavioral phenotypes associated with autism.

Microtine rodents, or voles, offer an excellent model for investigating the neuroendocrine and molecular mechanisms regulating affiliation and social attachment.¹ The social structures of voles vary greatly across species. For example, prairie voles (*Microtus ochrogaster*) are highly social and form long lasting pair bonds after mating. In contrast, montane vole (*M. montanus*) are relatively asocial, and do not form pair bonds. The neuropeptides oxytocin (OT) and vasopressin (AVP) play a critical role in regulating the social behavior of prairie voles. Central infusion of OT in female prairie voles during cohabitation with a male facilitates the formation of a partner preference.² While OT promotes pairbonding in females, AVP plays a similar role in male prairie voles. AVP facilitates, and a selective AVP receptor antagonist prevents partner preference formation.³

Analysis of the distribution of the OT and AVP receptors in the prairie vole brain provides insights into the possible cognitive mechanisms by which these neuropeptides may influence behavior. The OT receptor and the V1a vasopressin receptor are concentrated in the ventral forebrain, specifically in the nucleus accumbens and ventral pallidum, respectively. These structures are components of the mesolimbic dopamine reward pathway, which is thought to mediate the

rewarding and reinforcing properties of both natural stimuli and drugs of abuse. Infusion of OT antagonist into the nucleus accumbens prevents the formation of a partner preference in the female prairie vole.⁴ Furthermore, increasing AVP receptor expression in the ventral pallidum of a male prairie vole by using a viral vector facilitates pair bonding in male prairie voles.⁵ Interestingly, montane voles have few OT receptors in the nucleus accumbens and few AVP receptors in the ventral pallidum. Perhaps this species difference in receptor distribution may contribute to the species difference in behavior.

There are structural differences in the prairie and montane vole AVP receptor gene promoter that may account for the differences in receptor distribution and behavior.⁶ We created transgenic mice carrying the prairie vole genomic AVP receptor gene, including the promoter and these transgenic mice expressed the AVP receptor in a neuroanatomical pattern that was very similar to that of the prairie vole. Remarkably, these transgenic mice responded to AVP injections, like prairie voles by increasing their social interactions.⁶ These studies suggest that species differences in neuropeptide receptor expression in the brain may account for species differences in social behaviors. Therefore it is possible that individual differences in receptor expression in humans could contribute to behavioral differences characteristic of psychiatric disorders.

Given the modulatory effects of OT on behavior, we have begun using OT knockout mice to further investigate the role of this peptide in social behavior.⁷ OT knockout (OTKO) mice fail to remember recently encountered individuals despite apparently normal olfactory and general cognitive abilities.⁷ Social recognition in mice is measured by quantifying the duration of olfactory investigation in repeated exposures to the same stimulus mouse. Normal mice will show a decline in the amount of investigation time during subsequent exposures while OT knockout mice do not. Central injections of OT prior to the first encounter, but not after, completely rescue this very specific deficit and infusions of an OT antagonist inhibit social recognition in normal mice.⁸

In order to investigate the circuit modulated by OT to promote social recognition, we have used receptor autoradiography to localize the OT receptors in mouse brain, and Fos immunocytochemistry to examine neural activation during a social encounter. OT receptors are concentrated in several brain regions involved in social behavior in the mouse, including the olfactory bulbs, piriform cortex, amygdala and lateral septum.⁷ In normal mice, we found a significant induction of

Fos-immunoreactivity in each of these structures after a 5-min social exposure.⁸ *Fos* is an immediate early gene that is induced by neuronal activation and therefore allows the identification of brain regions activated during specific processes. OTKO mice show a normal induction of *c-Fos* in the olfactory bulbs, piriform cortex and cortical nucleus of the amygdala, but fail to show a normal neuronal induction in the medial amygdala. Instead, OTKO mice have a massive induction of somatosensory cortex and hippocampus activity which does not occur in normal mice. These data suggest that oxytocin may be acting in the medial amygdala during a social encounter to promote the proper processing of the social olfactory information, and the formation of a social memory. In the absence of OT, the olfactory information is processed by alternative neural circuits.

These findings in the OTKO mice parallel those reported in several, recent, human neuroimaging studies. The human amygdala is known to be involved in the processing of faces, emotional expression and social cues.⁹ When viewing images of faces, autistic subjects, compared to unaffected subjects, exhibit a decreased activation of both the amygdala and the cortical 'face' areas, and interestingly, also show an increase in other cortical regions typically activated while viewing non-social objects.^{10,11} Other studies have found that autistic patients have an impaired recognition memory for faces, dramatically lowered levels of plasma OT concentrations, and neuropathology within the amygdala.^{12,13} Thus, the amygdala and OT may play a conserved role in the regulation and retention of socially relevant stimuli, even across species utilizing different sensory modalities for processing the social environment.

Clearly animal models have much to offer for understanding the neural control of normal social behavior and may provide valuable insights into the potential etiologies of psychiatric disorders of social behavior. The studies presented here provide a strong argument for a role of OT and AVP in the regulation of specific, relevant social behaviors and therefore should be considered in research investigating the genetic, cellular and neural substrates of autism.

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